PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Imao MIKOSHIBA, et al.

Docket No: Q85257

Appln. No.: 10/519,102

Group Art Unit: 1614

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Examiner: Meghan R FINN

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For: DRUG COMPOSITION FOR BLOOD SUGAR CONTROL

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Yuji Kiyono, hereby declare and state:

THAT I am a citizen of Japan residing in Tokyo-to, Japan;

THAT I graduated from the Department of Biology, Faculty of Science, Shinshu University, Japan, in March of 1986.

Since April of 1986, I have been an employee of Kissei Pharmaceutical Co. Ltd., and I have been engaged in clinical development work on several compounds for the prevention or treatment of allergic, cardiovascular, diabetic or endocrinal diseases and the like at the Clinical Development department and Clinical Planning department of said company.

Particularly, from April of 2000 to March of 2003, I was engaged in clinical development work including monitoring and analyzing the results from a series of clinical studies of

mitiglinide calcium hydrate for an NDA (New Drug Application) filing for the treatment of diabetes.

I am one of the co-inventors of the subject matter of the above-identified application and I have knowledge of all aspects of the invention embodied therein.

The following study is one of the series of the above-mentioned clinical studies.

1. Object of the study

The clinical study of Example 4 described in the present specification was conducted to evaluate the administration timing for safe and effective oral administration before meals of mitiglinide calcium hydrate for the improvement of postprandial hyperglycemia.

2. Test drug

Placebo tablet: a tablet without any active ingredient.

Test drug tablet: a tablet comprising 10 mg of mitiglinide calcium salt hydrate (Chemical name: (+)-monocalcium bis[(2S, 3a, 7a-*cis*)-α-benzylhexahydro-γ-oxo-2-isoindolinebutyrate] dihydrate; Generic name: mitiglinide calcium hydrate).

3. Study design

Ten (10) healthy volunteers were administered the placebo tablet on Day 1 (Method 1), and the test drug tablet immediately (30 seconds) before meal on Day 2 (Method 2), 5 minutes before meal on Day 3 (Method 3), 10 minutes before meal on Day 4 (Method 4) and 30 minutes before meal on Day 5 (Method 5) as summarized in the following Table 1.

Table 1: Administration methods

Method	Test drug	Administration
Method 1	Placebo tablet	Administered immediately (30 seconds) before meal
Method 2	Test drug tablet	Administered immediately (30 seconds) before meal
Method 3		Administered 5 minutes before meal
Method 4		Administered 10 minutes before meal
Method 5		Administered 30 minutes before meal

Blood glucose levels and blood insulin levels were measured at each point of 40 minutes before meal (as baseline), 15 minutes before meal (only in Method 5) and 0 minutes before meal and 10, 20, 30, 45, 60 and 120 minutes after meal (in this DECLARATION, "before meal" means before starting the meal, "after meal" means after starting the meal and "baseline" means the value at 40 min before meal).

4. Results and Conclusions

4-1. Blood glucose level

The values at 0 minutes before meal in Methods 1 to 5 have already been described in Example 4 of the present specification. Including those values, the results of blood glucose level (mg/dL) are shown in the following Table 2 and Fig. 1 (see Attachment 1).

In Table 2, there is only one time for each Administration method and this is explained in Table 1. However, blood sampling for each Administration method took place at the various times as shown in Table 2.

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Table 2. Blood glucose level (mg/dL)

Administration method	Measurement point								
	min before meal			min after meal					
	40	15	0	10	20	30	45	60	120
1 (placebo)	86.5		85.6	92.6	111.5	123.2	115.9	103.6	86.2
2 (30 sec before)	86.2		87.0	92.3	105.1	94.1	79.0	66.7	81.4
3 (5 min before)	82.6		83.8	89.4	103.0	101.3	88.1	86.3	86.5
4 (10 min before)	85.7		84.2	82.7	95.6	98.2	87.3	79.7	86.5
5 (30 min before)	86.2	73.8	55.7	61.0	100.5	116.4	110.0	94.5	89.4

As shown in Table 2, in Method 5 (administered 30 min before meal), decreases in blood glucose level before meal were observed. That is, the blood glucose levels in Method 5 were 73.8 and 55.7 mg/dL at 15 min and 0 min before meal, respectively, and they were 12.4 and 30.5 mg/dL lower than the baseline (86.2 mg/dL), respectively. On the other hand, in Method 1 (placebo), 2 (administered 30 sec before meal), 3 (administered 5 min before meal) and 4 (administered 10 min before meal), the blood glucose levels before meal (85.6, 87.0, 83.8 and 84.2 mg/dL, respectively) were almost unchanged in comparison with the baseline (86.5, 86.2, 82.6 and 85.7 mg/dL, respectively). From these results, in my opinion administration within 10 min before meal will cause less hypoglycemic symptoms than administration 30 min before meal.

In addition, in Method 5 (administered 30 min before meal), postprandial blood glucose did not decrease in comparison with Method 1 (placebo). That is, the postprandial blood glucose levels in Method 5 were 116.4 mg/dL and 110.0 mg/dL at 30 min and 45 min after meal, respectively, and they were almost the same as that in Method 1 (123.2 mg/dL and 115.9 mg/dL, respectively), while the increases in postprandial blood glucose levels were suppressed in Methods 2, 3 and 4 (94.1 and 79.0, 101.3 and 88.1, and 98.2 and 87.3 mg/dL, respectively).

In conclusion, administration at 30 sec, 5 min or 10 min before meal is better than administration at 30 min before meal, because postprandial hyperglycemia was suppressed and a decrease in blood glucose level before meal did not occur.

4-2. Blood insulin level

The results of blood insulin levels are shown in the following Table 3 and Fig. 2 (see Attachment 2).

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Table 3. Blood insulin level (μU/mL)

Administration method	Measurement point								
	min before meal			min after meal					
	40	15	0	10	20	30	45	60	120
Method 1 (placebo)	4.35		4.45	17.18	38.94	54.34	45.81	36.44	15.68
Method 2 (30 sec before)	4.74		5.74	103.18	110.02	97.00	61.51	40.44	13.96
Method 3 (5 min before)	6.14		9.65	128.32	131.61	90.22	57.38	44.32	18.73
Method 4 (10 min before)	6.04		35.43	109.22	108.57	101.29	61.89	38.65	18.20
Method 5 (30 min before)	6.72	68.97	35.58	43.91	105.00	114.29	80.04	40.95	15.09

As shown in Table 3, any clinically meaningful increase of insulin levels before meal from each baseline was not observed in Method 1 (from 4.35 to 4.45), Method 2 (from 4.74 to 5.74) and Method 3 (from 6.14 to 9.65). On the other hand, insulin secretion occurred before meal in Method 5 (68.97 at 15 min before meal and 35.58 at 0 min before meal from the baseline of 6.72) and it is my conclusion that the insulin secretion before meal caused the decrease in blood glucose level before meal in Method 5.

In Method 4, insulin secretion started before meal (35.43 at 0 min before meal from the baseline of 6.04), although this insulin secretion did not cause a decrease in blood glucose level yet as shown in the above 4-1.Blood glucose level. From these results, in my opinion it is clear

that in case of administration earlier than 10 min before meal, insulin secretion will occur earlier and that will increase the possibility to decrease blood glucose level before meal.

Therefore, it is my opinion that the administration timing within 10 min before meal and the dose of 10 mg is an unexpectedly superior administration method to improve postprandial hyperglycemia with a lower probability to decrease blood glucose level before meal.

I believe that the significance of the administration timing of "within 10 minutes before starting meal" was unexpected without the results from the above-mentioned clinical study.

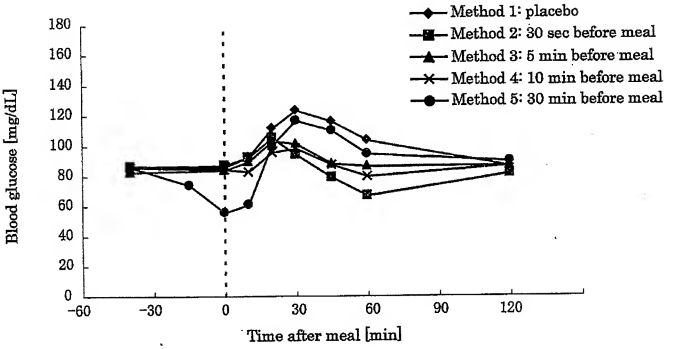
I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

December 5, 2008 Yuji Kiyono

Date Yuji Kiyono

Attachment 1

Fig. 1



Attachment 2

Fig. 2